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Bi-directional Brain-Systemic Interactions and Outcomes after TBI

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Abstract

Traumatic brain injury (TBI) is a debilitating disorder associated with chronic progressive neurodegeneration and long-term neurological decline. Importantly, there is now substantial and increasing evidence that TBI can negatively impact systemic organs including the pulmonary, gastrointestinal, cardiovascular, renal, and immune system. Less well appreciated, until recently, is that such functional changes can affect both the response to subsequent insults or diseases, as well as contribute to chronic neurodegenerative processes and long-term neurological outcomes. In this review, we summarize evidence showing bi-directional interactions between the brain and systemic organs following TBI and critically assess potential underlying mechanisms.

Keywords

Traumatic brain injury; neuroinflammation; microglia; bi-directional; systemic

Systemic Changes Following Traumatic Brain Injury

It has long been recognized that traumatic brain injury (TBI) can induce substantial systemic alterations that impact morbidity and mortality. TBI related changes in systemic organ function can affect both the response to subsequent insults or diseases, as well as to potentially contribute to chronic neurodegeneration and related neuropsychiatric dysfunction [1, 2]. Experimental and/or clinical studies have reported posttraumatic changes involving the systemic immune system, gut, lung, spleen, thymus, liver, heart and kidney [1, 2]. Potential mechanisms include activation of the hypothalamic-pituitary-adrenal (HPA) axis, alterations of the autonomic nervous system, immune system, microbiome and release of extracellular vesicles, among others [2–6].

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Declaration of Interests

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TBI is associated with a high rate of infections that exceeds that for other acute neurological conditions and that contributes to mortality. This includes both nosocomial infections in hospitalized patients, as well as subsequent increased susceptibility to infection, suggesting that TBI may compromise systemic immune function [7]. Experimental studies convincingly show considerable posttraumatic functional alterations in systemic immune cells, including those involved in both innate and adaptive immunity [5]. Posttraumatic immune changes continue chronically, contributing to neuroinflammation and associated neurodegeneration [5, 8–10].

Experimental reports demonstrate that posttraumatic infections and/or inflammatory challenges can increase chronic neuroinflammation and associated neurodegeneration, particularly in chronic neurodegenerative conditions, with exacerbation of neurological dysfunction [11–13]. These observations raise important therapeutic implications for the care of TBI patients.

Here we review brain-systemic interactions after TBI, both pre-clinical and clinical, addressing how they may influence recovery after injury. We underscore the potential mechanisms involved, the importance of systemic effects induced by TBI on outcome, and how such changes may require modifications in clinical care. Lastly, we suggest venues for possible therapeutic targeting.

Critical Assessment of Prior Work: Caveats

Although studies that address the systemic consequences of TBI have been accelerating and provide considerable evidence that such changes can critically affect outcome and future risk, there are important caveats regarding most published studies. Issues include: nature and clinical relevance of animal models used; injury severity and heterogeneity; potential sex differences; possible confounding effects of trauma; design issues for clinical research; and the general absence of conclusive evidence from human studies.

TBI is perhaps the most heterogeneous among central nervous system disorders. Critical confounding issues for interpretation of studies include injury severity, type of injury (focal, diffuse, penetrating), sex/gender, age, presence of co-morbidities, genetics/epigenetics, and prior injury. Concordantly, it is well known that the same clinical presentation may reflect highly different underlying pathology. Established animal models cannot fully reflect such diversity, but rather generally focus on selected aspects of clinical trauma such as contusion (controlled cortical impact, CCI), or more complex injury plus brain displacement (fluid-percussion, F-P), most often using only one level of severity. Even F-P models differ with regard to site of injury (lateral versus central), which cause very different physiological responses. Both CCI and F-P models require craniotomy but have the advantage of generating relatively consistent patterns of injury. In contrast, although certain closed injury models may be more clinically relevant, they induce more variable injury and require much higher animal numbers. Repeated head injury models usually utilize only mild injury and vary considerably as a function of numbers of insults and timing between injuries. Given constraints on use of most gyrencephalic animals, whose brain structure better parallels that of humans, most widely used models employ rodents, with mice often preferred because of size and availability of transgenic strains. Given model differences, it is often difficult to

compare studies across laboratories. Moreover, the predominant use of relatively simplistic animal models in lissencephalic species markedly adds to potential translational difficulties. To partially address such issues, some groups have attempted to replicate experimental results across species and/or use pathobiologically different models, either within or across laboratories.

Although it is well recognized that both mechanisms and outcomes may differ as a function of sex, the majority of reported studies have utilized animals of a single sex; this important issue may also confound and limit clinical translation.

Most clinical studies that examine systemic changes after TBI are retrospective, often with a small patient number. The relatively few prospective studies generally have methodological and conceptual limitations. Specifically, further investigation of how direct systemic trauma may complicate TBI outcomes will be important at a physiological level and in the identification of optimal therapeutic options for patients. This is particularly relevant in cases of severe TBIs where direct systemic trauma is more likely to occur. Given these caveats one must be cautious in interpreting much of the published work to date. Yet some of the consistent data being generated across experimental models and laboratories, as well as clinically, suggest opportunities for future mechanistic studies and translation, as well as for future therapeutic targeting and clinical care.

Immune system

TBI causes complex time-dependent changes in systemic and brain immune systems, affecting both innate and adaptive immune responses. Posttraumatic immune changes can persist chronically and contribute to morbidity/mortality after TBI [5, 14–16]. Clinically, TBI is associated with both innate and adaptive immune changes. There is evidence of increased circulating neutrophils following TBI [17]. During the early phase, neutrophils have enhanced reactive oxygen species (ROS) production [18, 19], but display impaired ROS generation more chronically following TBI. Furthermore, there are posttraumatic reductions in circulating monocytes [19] and natural killer (NK) cells [17], with decreased circulating T lymphocytes beginning within the first 24 hours following more severely injured patients [20, 21].

Pre-clinical studies also report significant TBI induced systemic immune responses. Following CCI in mice with moderate injury, there is mobilization of newly created myeloid cells (particularly neutrophils) into the blood, a decrease in T lymphocytes, atrophy of the thymus and defective T cell maturation [5]. Importantly, the posttraumatic circulating leukocytes showed functional changes, including alterations in leukocyte-derived reactive oxygen species (ROS) production in monocytes and neutrophils, cytokine production, and phagocytic ability [5]. Similarly, in a closed head injury model, trauma caused a significant loss of thymocytes as early as 3 days following injury; blood monocytes were reduced at 1 day following injury and remained suppressed up to 1 month [22]. Overall, these clinical and preclinical findings show that TBI suppresses both innate and adaptive immune responses.

Gastrointestinal (GI) System

TBI patients often experience alterations in GI function including upper GI intolerance, intestinal barrier disruption and intestinal tract dysmotility (Figure 1, Key Figure), which can affect posttraumatic morbidity and mortality [23–26]. Experimental TBI models demonstrate motility and permeability changes occurring within several days following mild-severe injury [12, 27]. In *drosophila*, TBI also caused intestinal barrier dysfunction associated with increased mortality [28]. Some models show early effects, including transient changes in small bowel permeability, but increased colonic permeability was reported in mice beginning several days posttrauma and persisting through 28 days [12]. Increased colon permeability can allow access of pathogenic bacteria or bacterial toxins to the systemic circulation, potentially causing endotoxemia and/or systemic toxicity. Delayed intestinal permeability changes also occur clinically and correlate with injury severity [23]. Permeability changes are associated with systemic inflammatory response syndrome, multiple organ failure and infections [23].

Mice subjected to moderate CCI show increased paracellular permeability at 28 days, associated with decreased expression of claudin-1 at both mRNA and protein levels [12]. CCI also induced pathological changes in the colon, with thickening of smooth muscle and greater mucosal depth, as well as increased expression of GFAP and Sox 10 in glial cells. When subsequently subjected to infectious colitis by *Citrobacter rodentium* at 6 weeks after injury, injured animals demonstrated greater progressive neuroinflammation and neurodegeneration changes as compared to non-infected TBI animals (Figure 1) [12]. Posttraumatic intestinal mucosal damage with permeability changes, as well as increased expression of inflammatory cytokines in the intestine and plasma endotoxin levels, have been observed in mice deficient for nuclear factor erythroid 2-related factor 2 (Nrf2), suggesting a potential protective role for Nrf2 [29]. Furthermore, delayed decreases of contractile activity in the ileum was found at 7 days after rat CCI, with reduced transit time; intestinal smooth muscle showed edema and increased expression of inflammatory cytokines [27].

More recently, our group has demonstrated that induction of a chemical colitis with dextran sodium sulfate (DSS) - a well characterized mouse model - beginning 6 weeks after CCI, also increases posttraumatic neuroinflammation, neurodegeneration and neurobehavioral dysfunction; this occurred both in mild, as well as moderate-severe injury [30]. Together, these observations appear consistent with studies of sickness behavior, in which systemic inflammation can lead to brain inflammation and functional alterations, particularly following a primary brain insult or disorder causing neurodegeneration [31]. Consistent with this concept, systemic immune challenge with LPS exacerbated neurological dysfunction in a midline fluid-percussion model (mFPI) [13].

Future studies should further delineate the time course of immune/inflammatory responses in both the gut and brain following TBI. Moreover, as pre-clinical investigations in these areas have often focused on male animals and given recognized sex-dependent differences in immune responses [32], further studies should address potential sex-dependent differences for development and progression of TBI-induced brain-gut interactions.

There has been growing interest in the influence of the microbiome on brain function and dysfunction, including after TBI. Following CCI in mice, bacterial changes (dysbiosis) were observed in the gut or feces in several studies [33–36]. Following repetitive mild TBI in mice, transient microbiome changes were reported [33]; however, repetitive mild TBI rats showed decreased gut microbial diversity from 6h to 30 days [34]. Given the methodological challenges in following posttraumatic microbiota changes in mice, such as the need to individually house mice because of confounding effects of coprophagia (with resulting stressor effects), as well as injury model, mouse strain and severity differences, comparison of results across studies must be interpreted cautiously.

Other work has sought to administer protective bacteria to alter the microbiome in order to improve outcomes [37, 38] or begun to examine the impact of aging on the microbiome and brain injury. The aged microbiome shows increased pro-inflammatory cytokines, and modifying the microbiome in young animals to that of an aged phenotype through fecal gavage exacerbated outcomes after experimental stroke [39]. This study has potential implications more generally for neurodegenerative disorders, including TBI, where poorer outcomes are observed with aging [40]. To what extent the microbiome may contribute to chronic neurotoxic inflammation - an important component of TBI and chronic neurodegenerative disorders - requires further study.

Lung

Hospitalized patients with TBI frequently show lung damage, with a prevalence greater than 20% that has increased in the past 20 years [41]. Moreover, there is a high incidence of infections in TBI patients that appears to correlate with injury severity [7, 42]. Among cases of patients with infection, most involve lung pathology, with pneumonia occurring in 30–50% of those who develop nosocomial infections [42]. Such individuals have increased mortality and disability. However, various risk factors may influence infections rates after head injury [42, 43]. For example, admission to an intensive care unit (ICU) and more prolonged ICU stays increase infection risk [44]. Several groups have examined the effects of experimental TBI on lung physiology and function. Closed head injury in rats caused pulmonary edema, protein leakage and increased inflammatory cytokines in alveolar fluid [45]. Acute lung injury was also reported following CCI in mice [46]. The latter study also demonstrated that extracellular vesicles (EV) containing inflammasome proteins were released after clinical TBI into the serum and caused lung injury; moreover, blocking EV uptake or using monoclonal antibodies to inhibit inflammasome activation protected against posttraumatic lung injury (Figure 1) [46]. More recently, the same group showed that treatment with a low molecular weight heparin limited the posttraumatic inflammasome response in both brain and lung, reducing lung injury [47]. A separate recent study reported that TBI increased lung permeability and monocyte infiltration at 24 hours after moderate mouse CCI [11]. Importantly, both clinical and experimental studies demonstrate that pathological pulmonary changes after TBI are associated with increased levels of high mobility group box 1 (HMGB1) in serum or plasma [46, 48]. Moreover, experimental evidence suggests that this may result from damage to neurons or endothelial cells in the blood-brain-barrier (BBB), with subsequent induction of inflammation [48].

Similar to GI studies, bacterial infection within the lung after experimental TBI exacerbates neuroinflammation, as well as neurological dysfunction (Figure 1) [11]. In one study, for instance, following moderate CCI, mice were infected with Streptococcus pneumoniae either early (3 days) or late (60 days) after injury. Infection at either time increased mortality, neuroinflammation and motor dysfunction [11]. Monocyte infiltrates in the lung early after injury showed evidence of immunosuppression, with reduced expression of inflammatory cytokines and reactive oxygen species (ROS). In contrast, delayed infection showed higher expression levels of both inflammatory cytokines and ROS as compared to sham infected animals. Intratracheal administration of LPS after CCI injury in mice can also exacerbate posttraumatic cognitive impairment [49]. These experimental models differ from ventilator-associated pneumonia, which is commonly found in severely injured TBI patients and is associated with a poor prognosis [50]. Collectively, these studies demonstrate important bi-directional effects between the lung and the brain that potentially impact TBI outcomes [11]. They also suggest that chronic TBI patients should be closely followed for evidence of systemic infections, and if present, treated aggressively. However, to better understand these interactions, future studies should delineate the effects of injury severity, infection model, pre-existing co-morbidities, and sex differences.

Heart

Cardiac complications appear to be relatively common after moderate to severe TBI. Clinical studies in this context have largely been retrospective. Specifically, two major trauma groups reported detectable or elevated serum cardiac troponin I (cTnI) levels in approximately 30% of TBI patients (420 and 580, respectively), which were associated with increased mortality [51, 52]. A more recent, prospective study found that nearly 60% of patients showed detectable cTnI levels; again increased levels were a predictor of mortality [53]. Although intriguing and potentially important, future studies should further delineate relationship to injury severity, presence of major polytrauma and be sufficiently powered to address issues such as age, sex/gender and presence of known co-morbidities.

A mouse CCI study reported significant reductions in posttraumatic cardiac function at 3 and 30 days, with decreased left ventricular ejection fraction (LVEF) (Figure 1) [54]. However, findings from clinical studies have been mixed. In one report, 5 of 15 patients with moderate-severe TBI showed reduced systolic function [55]. Another study examined 46 patients with moderate-severe TBI; the authors reported cardiac dysfunction in 6 of the patients (13%), with a mild to moderate reduction of LVEF, although cardiac changes were not associated with adverse outcome [56]. A larger study involving 139 patients with isolated TBI found 12% with reduced LVEF; an abnormal echocardiogram was associated with mortality [57]. Yet in a prospective study of 20 severe TBI patients, LVEF did not differ from controls, although diastolic function was slightly lower in the injury group [58].

Overall, these clinical and pre-clinical studies provide some support for the conclusion that more severe TBI can negatively impact cardiac function. When present, increased cardiac troponin I levels appear to predict worse outcome. Although no mechanism has been established, the excessive sympathetic activity observed in these patients may be a key factor.

Other Organs

More limited information is available regarding TBI's impact on other systemic organ systems, such as the kidney or liver (Figure 1). One retrospective clinical review of 207 TBI patients with moderate-severe injury reported acute kidney injury (AKI) in 9% of the patients; higher rates were found in older patients and those with more severe trauma [59]. Another study reported that plasma obtained from patients with severe TBI and evidence of subclinical kidney injury could induce cellular dysfunction and apoptosis in cultured human renal proximal tubular epithelial cells [60]. Several retrospective studies have identified potential biomarkers for assessment of TBI severity and the occurrence of AKI including: liver-type-fatty acid-binding-protein (L-FABP) [61]; procalcitonin (PCT) [62]; and urinary neutrophil gelatinase-associated lipocalin (NGAL) [63]. Additionally, diffuse brain injury in rats is associated with renal hypoxia [64].

TBI can activate acute phase responses in the liver early after injury [65, 66]. Liver expression of serum amyloid A (SSA) peaked 1 day following injury in both male and female mice; SSA mRNA and protein expression co-localized with astrocytes and macrophage/microglia in discrete brain regions in a sex-dependent manner [67]. Fluid percussion injury in rats induced hepatic inflammation and oxidative stress at 24h following injury [68]. However, the impact of changes in these organs on long term behavioral outcomes or neurodegeneration requires further study.

Bidirectional Interactions and TBI: Potential Mechanisms

A number of potential mechanisms have been suggested or implicated in TBI-associated systemic alterations. Historically, most emphasis has been placed on the role of the hypothalamic-pituitary- adrenal (HPA) axis, the autonomic nervous system (ANS) and the immune system.

Acute activation of the HPA can alter cortisol and multiple endocrine factors; resultant physiological changes can affect, among others, immune function and metabolism [1, 2].

Glucocorticoids (cortisol in humans and corticosterone (CORT) in rodents) are the main effectors of the HPA axis and exert potent immunosuppressive effects through activation of the glucocorticoid receptor [17, 69]. Both clinical and preclinical studies show alterations in HPA function following TBI [70–72]. Patients with mild- to moderate-level TBI have increased circulating cortisol for 2 days following injury, whereas severely injured patients have decreased circulating cortisol at 1–3 days [73]. Such differential responses have also been shown experimentally. Rodents subjected to mild-level CCI show heightened restraint-induced CORT at 34 and 70 days post-injury [74]; in contrast, restraint-induced CORT responses were significantly more blunted in moderate CCI versus mild level CCI at 7 and 35 days following injury [75]. In addition, sex-dependent effects have been reported in HPA axis responses; male mice exposed to mild blast TBI had increased restraint-induced CORT at 7 and 10 days post-injury, whereas females displayed the opposite response [76]. Increased microglia activation in the paraventricular nucleus (PVN) was reported in male, but not female animals, following midline F-P [77]. Such sex-dependent effects on TBI-induced alterations of HPA activation may have important implications for outcomes.

Adrenal insufficiency (AI) occurs in about a quarter of TBI patients, likely due to HPA axis dysfunction [78, 79]. In addition, many patients with severe TBI demonstrate abnormal circulating levels of glucocorticoids in response to pharmacologically-induced stress within 10 days following injury [79]. Experimentally, in a closed head injury model, there was a decreased number of circulating lymphocytes (particularly T cells) with changes inversely correlated with plasma CORT [80]. Elevated CORT has also been associated with lymphocytopenia after experimental stroke [81]. Given that brain-induced immunosuppression makes patients more vulnerable to infections [82] and the known effects of HPA axis dysfunction on immune and endocrine responses, additional mechanistic studies should be performed to address implications for therapeutic interventions and patient care.

Paroxysmal sympathetic hyperactivity (PSH, sympathetic storm) has been implicated in diverse peripheral pathophysiologic effects after acute brain injuries [3]. Beta blockers have been examined clinically to modulate systemic organ pathological changes after TBI, with limited evidence for improvement in mortality but no data relating to impact on functional outcomes [83–85]; overall, because of study design issues the level of evidence supporting therapeutic benefit has been considered low [82]. A randomized study [84] purported to demonstrate reduced mortality and better longer-term clinical outcomes in TBI patients following administration of the beta blocker Propranolol, but it is important to note that the study was unblinded, lacked placebo controls and actually showed no significant benefit on primary outcomes. Collectively, these studies suggest that ANS mediated effects are more complex and nuanced than may initially seem. Although activation of the sympathetic nervous system has been implicated in inflammation, such as through effects in the spleen and liver [86], it can also control resolution of inflammation [87]. In addition, the parasympathetic nervous system may have a role in modulating inflammation [88].

TBI results in both early and late systemic immune changes, which appears to contribute to chronic neuroinflammation and neurodegeneration (Figure 2). Expression of toll-like receptor (TLR)4 on myeloid cells that enter the brain in the early period after TBI may affect longer-term adaptive immune responses [89]. Immune cell changes after brain injury substantially parallel those observed with normal aging and suggest that TBI may accelerate immune aging or senescence [5, 40]. A possible mechanistic role for circulating monocytes in posttraumatic toxic neuroinflammation after TBI has been supported by the work of several groups [14, 90–92]. This mechanism appears to be exaggerated in aged animals [92]. Global depletion of monocytes, as well as knock-out or inhibition of peripheral C-C chemokine receptor type 2 (CCR2(+) monocytes, reduce posttraumatic neuroinflammation, and neurobehavioral responses in both juvenile and aged mice [14, 90, 92].

Clinically, TBI increases plasma levels of inflammatory factors such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein (CRP). TBI substantially elevates both numbers of circulating leukocytes and their expression of TNF-α and inducible nitric oxide synthase (iNOS); induces greater free radical production in leukocyte homogenates; and elevates expression of iNOS, cyclooxygenase (COX)-2 and NADPH oxidase (gp91(phox)) in circulating leukocytes [19]. Moreover, after injury circulating neutrophils show markedly up-regulated oxidative activity and suppressed phagocytic ability [19]. In a recent clinical

study, patients with mild TBI had altered plasma cytokine levels that persisted up to one year post injury [93].

Microglial activation, as well as infiltration of myeloid cells after experimental TBI, are implicated in posttraumatic neurotoxic neuroinflammation [15, 16, 91, 94]. In mice, these responses are sexually dimorphic, with males showing greater and earlier myeloid infiltration than females, as well as dissimilar cytokine responses [95, 96]. These differences are associated with less pathological changes in female animals during the early period after injury [95]. Moreover, posttraumatic brain injury responses are exacerbated in aged mice, with evidence of greater oxidative stress responses and greater microglial functional changes - including altered phagocytosis and increased senescent markers [40, 97]. Pro-inflammatory microglial activation persists chronically, both clinically and in experimental brain trauma models over months to years [16, 94, 98, 99]. Chronic changes in TBI-induced systemic immune responses include alterations in bone-marrow derived myeloid cells. These effects, as well as chronic alterations in microglia, may reflect in part epigenetic changes that may be modifiable (Figure 2) [5, 94]. Further research is needed to better characterize sex and age dependent differences in immune responses to TBI, both peripheral and central, as well as their potential bi-directional interactions across experimental models.

Recently, it has been shown that posttraumatic microglial activation leads to the release of extracellular vesicles (EVs) in the blood, both at early periods and more chronically. These EVs contain pro-inflammatory factors, including micro RNAs (miRs), that can potentially affect systemic organs [4, 100–102]. EVs appear to play a role in the propagation of neuroinflammation and in promoting neurodegeneration at more distant sites [101]. They may also serve as a mechanism for both physiological and pathophysiological interactions between the brain and other organ systems [100–102]. In mice, CCI increased EVs (microparticles) in blood at 24h [101]. Enriched EVs from posttraumatic blood samples activated microglia *in vitro*, and like LPS- activated BV2 cells (which upregulate pro-inflammatory factors including miRs) caused propagation of neuroinflammation in the brain of uninjured mice after a stereotaxic cortical injection [101]. Another group also reported increased plasma EVs after CCI injury and demonstrated that enriched EVs from LPS stimulated macrophages, injected systemically, increased microglial activation and lesion volume after TBI [4]. Exosomal proteins were measured from blood samples of 21 patients with moderate-severe TBI; observed changes suggested potential prognostic value [102]. Another clinical study reported significantly increased serum EVs after severe TBI, with even larger changes in patients showing evidence of lung injury [100]. Using an epithelial cell line *in vitro*, administration of these EVs led to inflammasome activation and pyroptosis, implicating EVs in posttraumatic lung injury [100]. A study of patients with mild or repeated mild TBI showed dysregulated exosomal miRs in blood long after injury, potentially providing a method to help understand persisting neurological symptoms in such patients [103]. Whether EVs can serve as a therapeutic target or treatment has also begun to be addressed in pre-clinical models. Treatment with a neutral sphingomyelinase inhibitor, reduced EV release and downregulated pro-inflammatory factors induced by LPS treatment of BV2 microglia *in vitro*. Treatment with sphingomyelinase inhibitors reduced gene expression of multiple pro-inflammatory markers associated with microglial activation in brain after CCI injury [104]. Potential for therapeutic use of exosomes was also recently

demonstrated. Exosomes from bone marrow mesenchymal stem cells administered retro-orbitally 15 minutes after CCI in mice decreased the inflammatory response, lesion size and functional outcomes [105].

Concluding Remarks

Although it has long been recognized that TBI patients have unusually high infection rates and evidence of changes in various systemic organs, more recent clinical and pre-clinical research has underscored the importance of brain-systemic interactions for TBI outcomes. Experimental work shows that such interactions have bi-directional implications with regard to secondary posttraumatic neuroinflammation and progressive neurodegeneration. TBI causes both acute and chronic systemic immune changes, which mimic, in part, those observed during aging, and can increase potential susceptibility to infection. TBI-related pathological changes occur in multiple systems and organs - including the immune system, intestine, lung and heart. Posttraumatic infections in the pulmonary or GI systems, or non-infectious inflammation in the lung, gut or systemic circulation appear to exacerbate chronic tissue damage and neurobehavioral deficits after head injury.

Mechanistic studies have begun to identify potential therapeutic targets to limit the consequences of these pathogenic brain-systemic changes. However, many questions remain to be addressed (see also “Outstanding Questions”). Among the pathological consequences of TBI-mediated effects in systemic organs, which are the most important with regard to clinical outcomes, and can they be successfully targeted to improve mortality and to facilitate recovery? Are the various changes in systemic organ function after injury additive or synergistic with regard to detrimental impact? Given the multiple proposed mechanisms for brain-systemic interactions that have some experimental support, which are most likely to be modifiable to alter outcome? Can systemic effects of TBI be used as biomarkers for mortality or functional recovery, and if so, can concurrent use of multiple systemic markers enhance predictive accuracy? As TBI appears to accelerate markers of aging, especially with regard to immune changes, can strategies used to modify “inflammaging” provide therapeutic benefit for TBI? Finally, in this emerging research area, as for many others, important sex differences have been observed, and if these translate to humans, it is possible in clinical settings, male and female patients may necessitate different evaluation or treatment approaches.

There is growing recognition, then, that brain trauma results in important systemic changes, many of which may influence outcome. From a clinical perspective, these insights should ultimately impact how such patients are followed and treated. Although animal TBI models, taken individually, may have relatively limited translational relevance, research findings - especially if confirmed across models and species may suggest novel therapeutic and biomarker targeting, as well as modify how head injured patients are monitored and treated.

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Outstanding Questions Box

- Among the pathological consequences of TBI-mediated effects in systemic organs, which are most important with regard to clinical outcomes?
- Are the various changes in systemic organ function after injury additive or synergistic with regard to detrimental impact?
- Given the multiple proposed mechanisms for brain-systemic interactions that have some experimental support, which are most likely to be modifiable to alter outcome?
- Can systemic effects of TBI be used as biomarkers for mortality or functional recovery? And if so, can concurrent use of multiple systemic markers enhance predictive accuracy?
- As TBI appears to accelerate markers of aging, especially with regard to immune changes, can strategies used to modify “inflammaging” provide therapeutic benefit for TBI?
- Are there sex differences in the pathological consequences of TBI that may necessitate different evaluation or treatment approaches for male and female patients?

Highlights

- Traumatic brain injury (TBI) can cause significant changes in systemic organ function
- Peripheral immune challenges following TBI can increase chronic neuroinflammation and exacerbate neurological dysfunction
- Recognition of brain-systemic interactions after TBI provides important insights relating to the pathobiology and treatment of head injury
- Targeting brain systemic changes after TBI may influence long-term morbidity and mortality

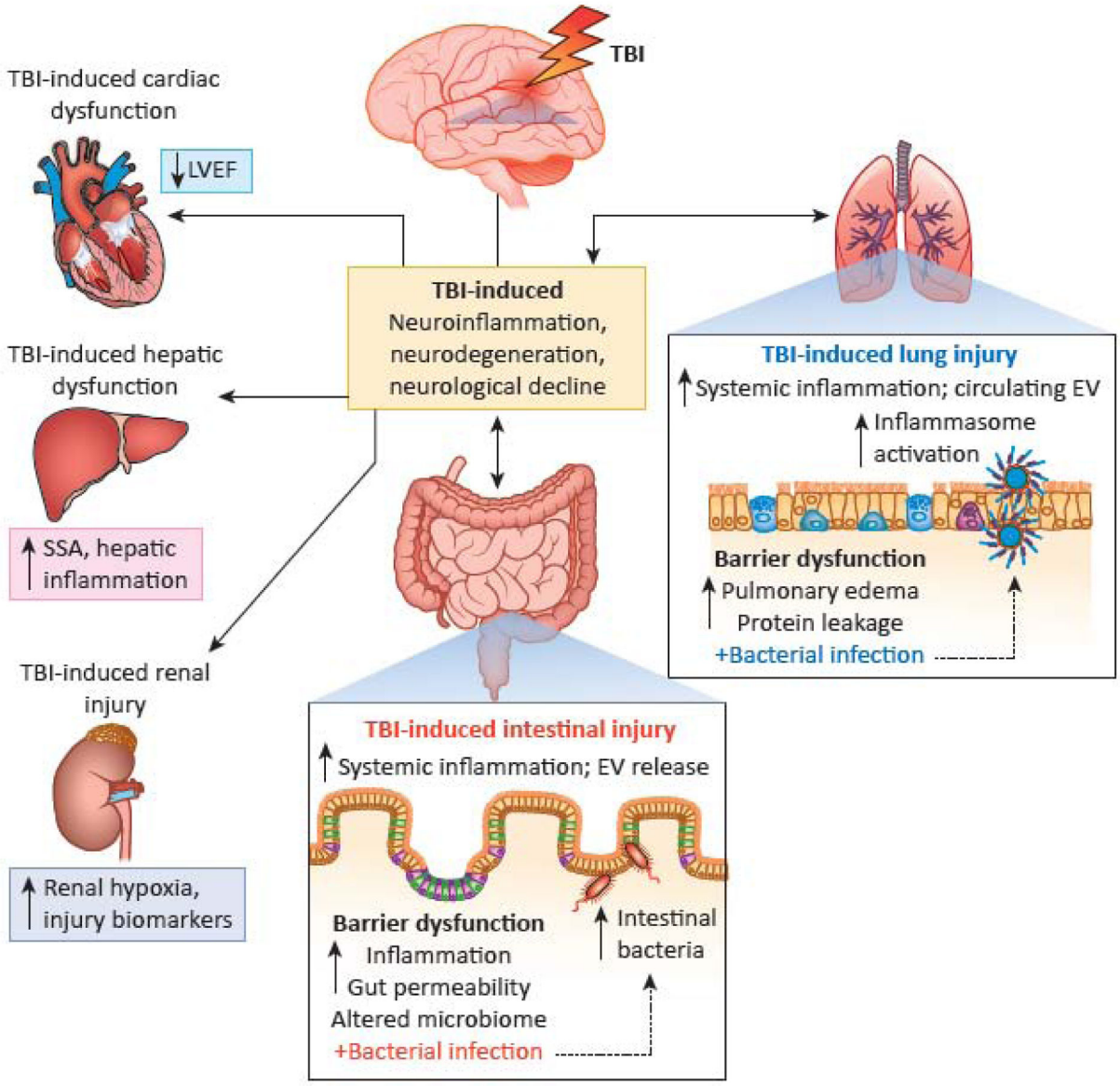

Figure 1: Bi-directional effects of TBI and systemic organs.

TBI can induce lung and intestinal injury (right-side and bottom insets, respectively). This in turn can lead to organ dysfunction and subsequent increases in systemic inflammatory responses including EV release. Subsequent bacterial insults to both the lung and gut may result in exacerbation of TBI-induced deficits including neuroinflammation, neurodegeneration and neurological decline. In addition, TBI can result in cardiac, hepatic and renal dysfunction which may increase mortality (left-side column); however, the subsequent effects on long-term neurological function remain to be determined.

Abbreviations: Traumatic brain injury (TBI); Extracellular vesicles (EV); Left ventricular ejection fraction (LVEF); Serum amyloid A (SSA).

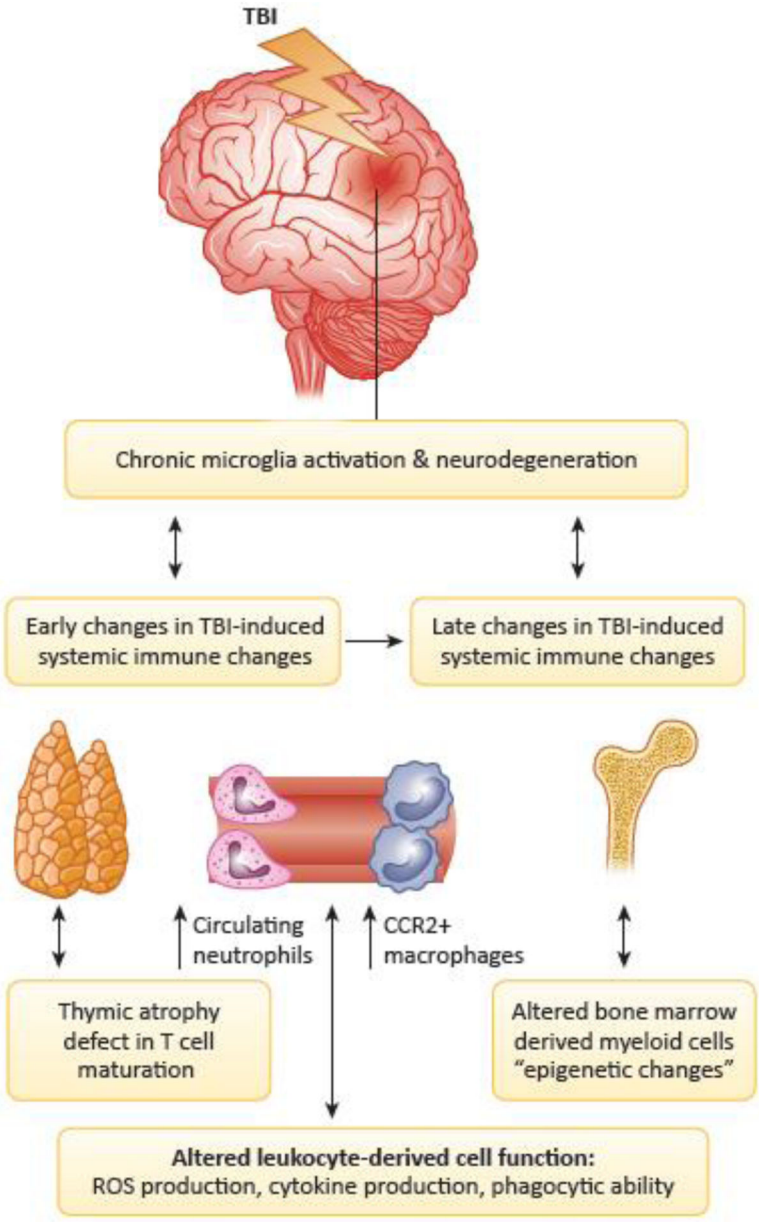

Figure 2: TBI-induced alterations in systemic and central immune function.

During the early stages of TBI, alterations can emerge in the systemic innate and adaptive immune responses that can in turn alter TBI-induced microglia responses and subsequent neurodegenerative processes. In addition, TBI can induce late changes in systemic immune responses including altered bone-marrow-derived myeloid cell function, which may in turn alter chronic microglial responses and neurodegenerative processes. Abbreviations: Traumatic brain injury (TBI); Reactive oxygen species (ROS); C-C chemokine receptor 2 (CCR2).